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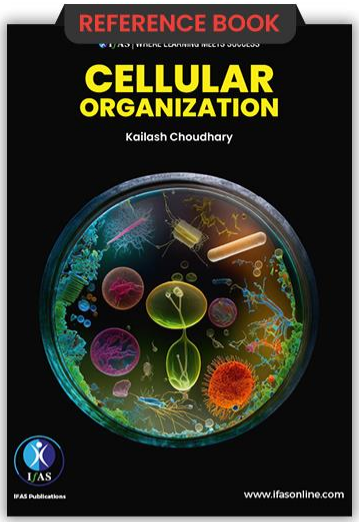
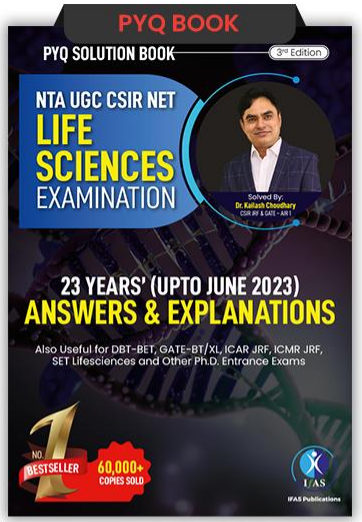
CSIR NET – Life Science

Unit 2: Cellular Organization

L6

Transport of Large molecules

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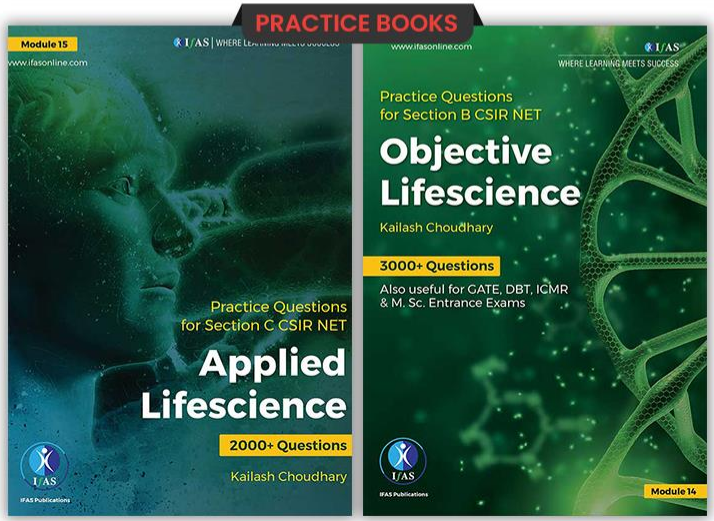

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Points to be covered in this Lecture

- Transport of macromolecule, Endocytosis
- Receptor mediated endocytosis - LDL, Transferrin
- Trans-cytosis
- Electrical properties of membrane

Transport of macromolecule

Endocytosis

→ uptake of macromolecule

Non Specific

- Phagocytosis
- Pinnocytosis

Clathrin Dependent

Clathrin independent

Specific

- Receptor mediated endocytosis

• Clathrin Dependent

Exocytosis

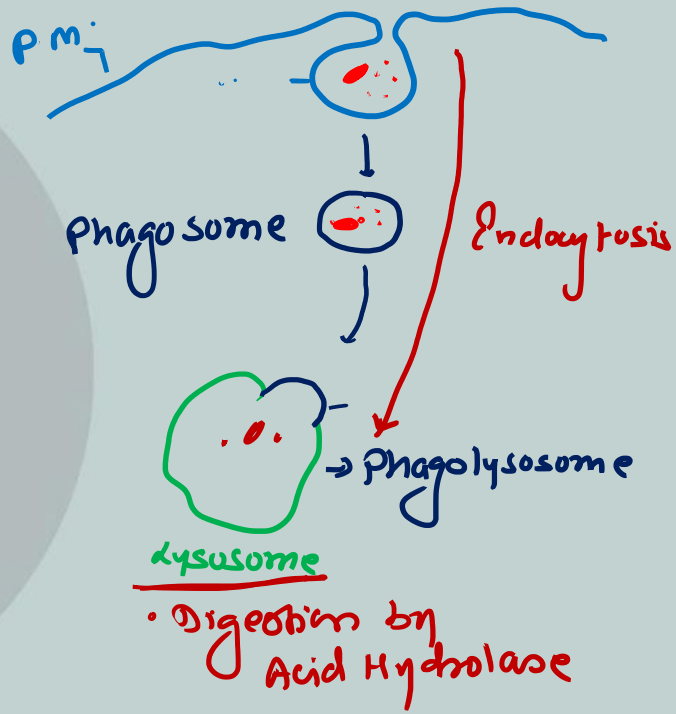
• Secretion of cell

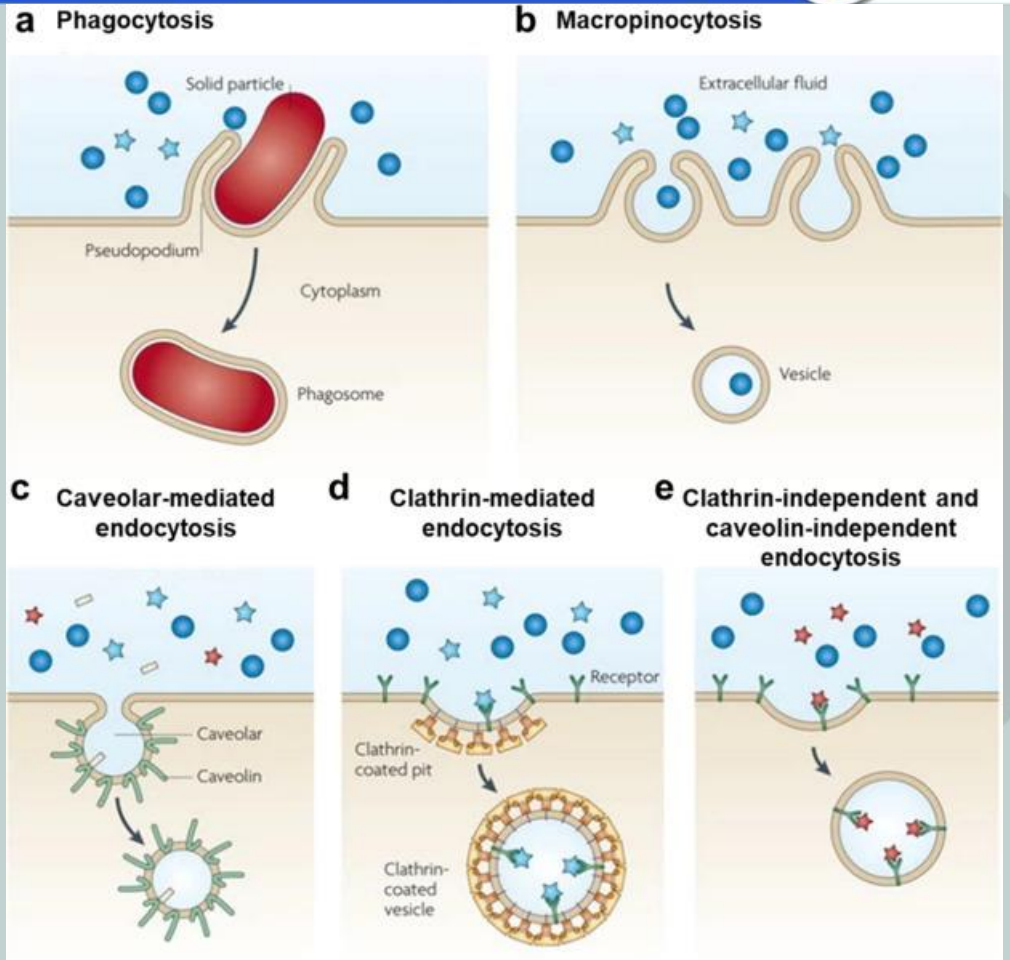
Transcytosis

• Endocytosis from one side & Exocytosis from another site

Endocytosis – term Christian de Duve in 1963

- Take up macromolecules and particles from the surrounding medium
- Material to be internalized- surrounded by an area of plasma membrane, which then buds off inside the cell to form a vesicle containing the ingested material.
- Include both the ingestion of large particles -such as bacteria - known as phagocytosis (cell eating)
- Uptake of fluids or macromolecules in small vesicles take place in all eukaryotic cells. → Pinnocytosis

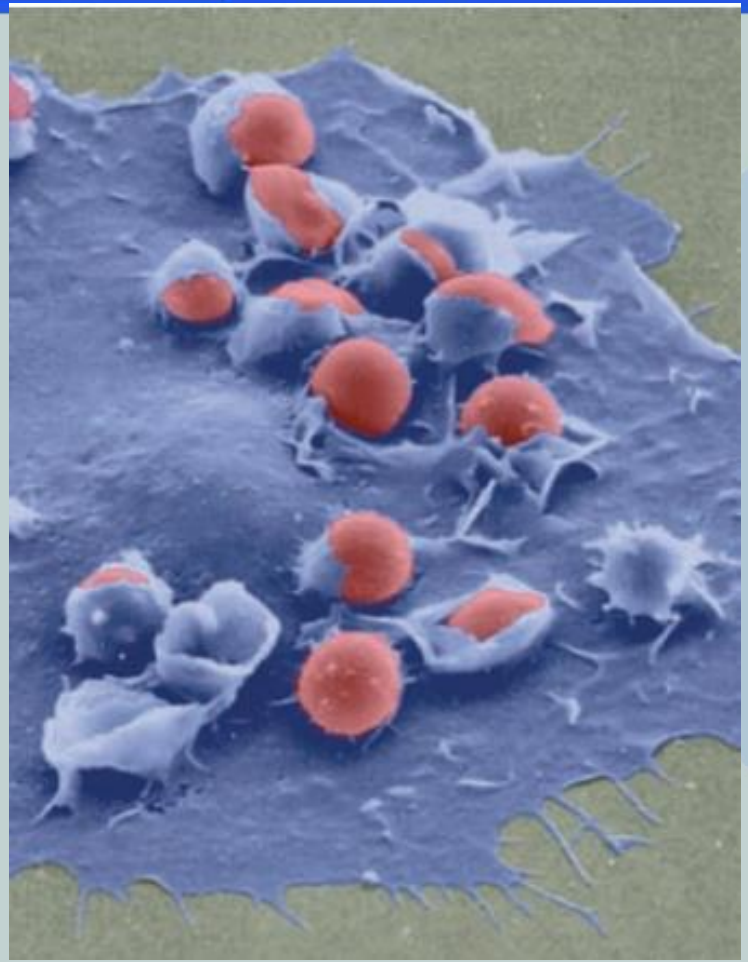



a Phagocytosis
Solid particle
Pseudopodium
Cytoplasm
Phagosome
b Macropinocytosis
Extracellular fluid
Vesicle
c Caveolar-mediated endocytosis
Caveolar
Caveolin
d Clathrin-mediated endocytosis
Receptor
Clathrin-coated pit
Clathrin-coated vesicle
e Clathrin-independent and caveolin-independent endocytosis

Non Specific

1. Phagocytosis – cell eating

2. Pinnocytosis – cell drinkng



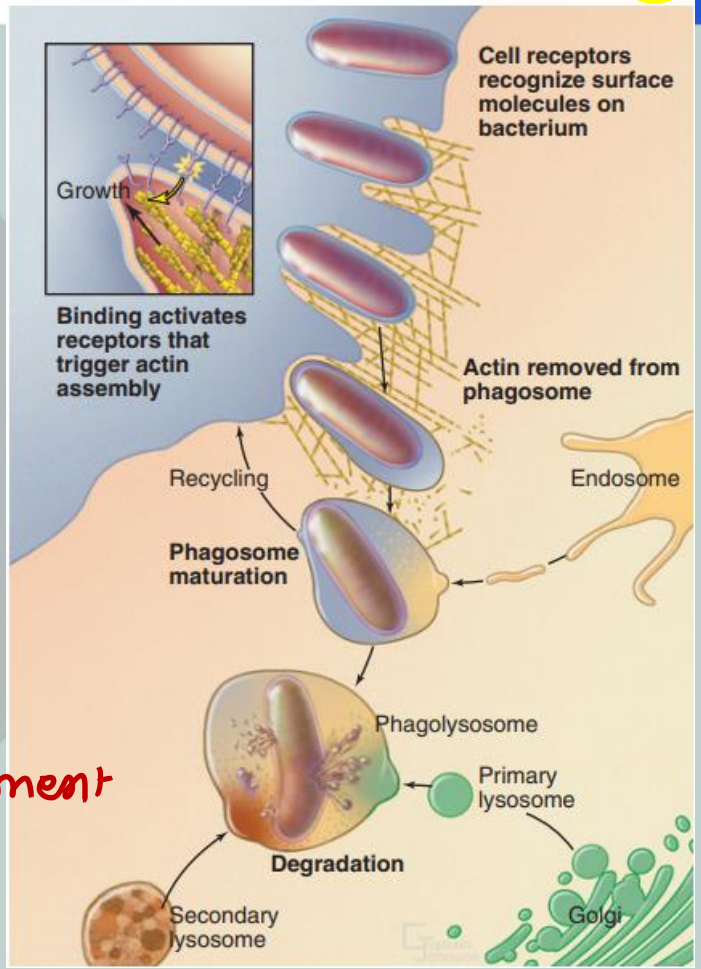
Scanning electron micrograph of a macrophage ingesting red blood cells

- **Phagocytosis** proceeds through four steps:

1. attachment,
2. engulfment, → Actin involve helps to change the shape.
3. fusion with lysosomes, and
4. degradation.

- These steps are highly regulated by cell surface receptors, polyphosphatidylinositides,

- and signaling cascades mediated by Rho-family guanosine triphosphatases (GTPases) → Actin rearrangement



In mammals, phagocytosis of microorganisms is the function of three types of white blood cells—

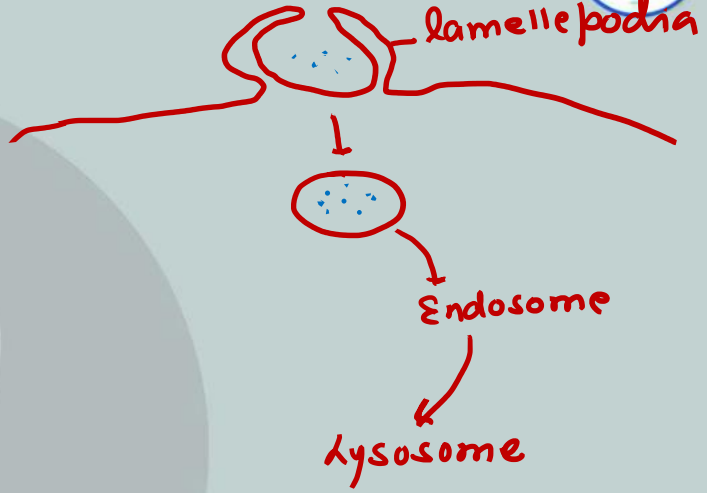
1. macrophages,
2. neutrophils, and
3. dendritic cells

which are frequently referred to as "professional phagocytes

Provide Defence

Macropinocytosis is the uptake of extracellular fluids, rather than particles, in large vesicles (0.2–10 µm in diameter).

- Like phagocytosis, macropinocytosis results from actin-based movements of the plasma membrane,
- in this case leading to the formation of lamellipodia (sheetlike projections of the plasma membrane.

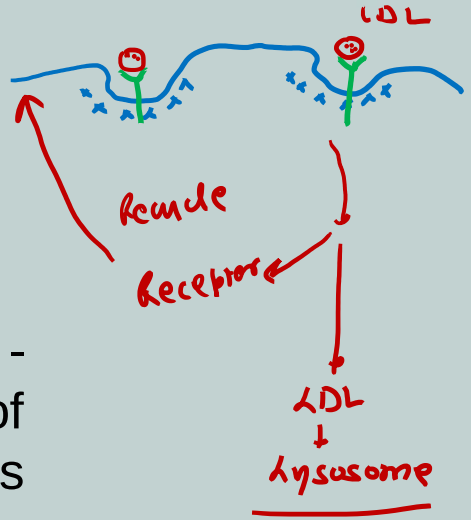


Specific Endocytosis

Receptor mediated endocytosis –

- The uptake of cholesterol by mammalian cells
- Clathrin-mediated endocytosis
- Michael Brown and Joseph Goldstein demonstrated - uptake of LDL by mammalian cells requires the binding of LDL to a specific cell surface receptor that is concentrated in clathrin-coated pits and internalized by endocytosis.
- The receptor is then recycled to the plasma membrane while LDL is transported to lysosomes where cholesterol is released for use by the cell

Example



Cholesterol - Lipoprotein = Lipid + Protein

→ Protein without lipid is k/a Apolipoprotein

- Lipid & Protein Ratio determines the density of lipoprotein

HLDL – ~~Low~~ High density lipoprotein → Protein↑ : lipid ↓ = Density ↑ = Good Cholesterol

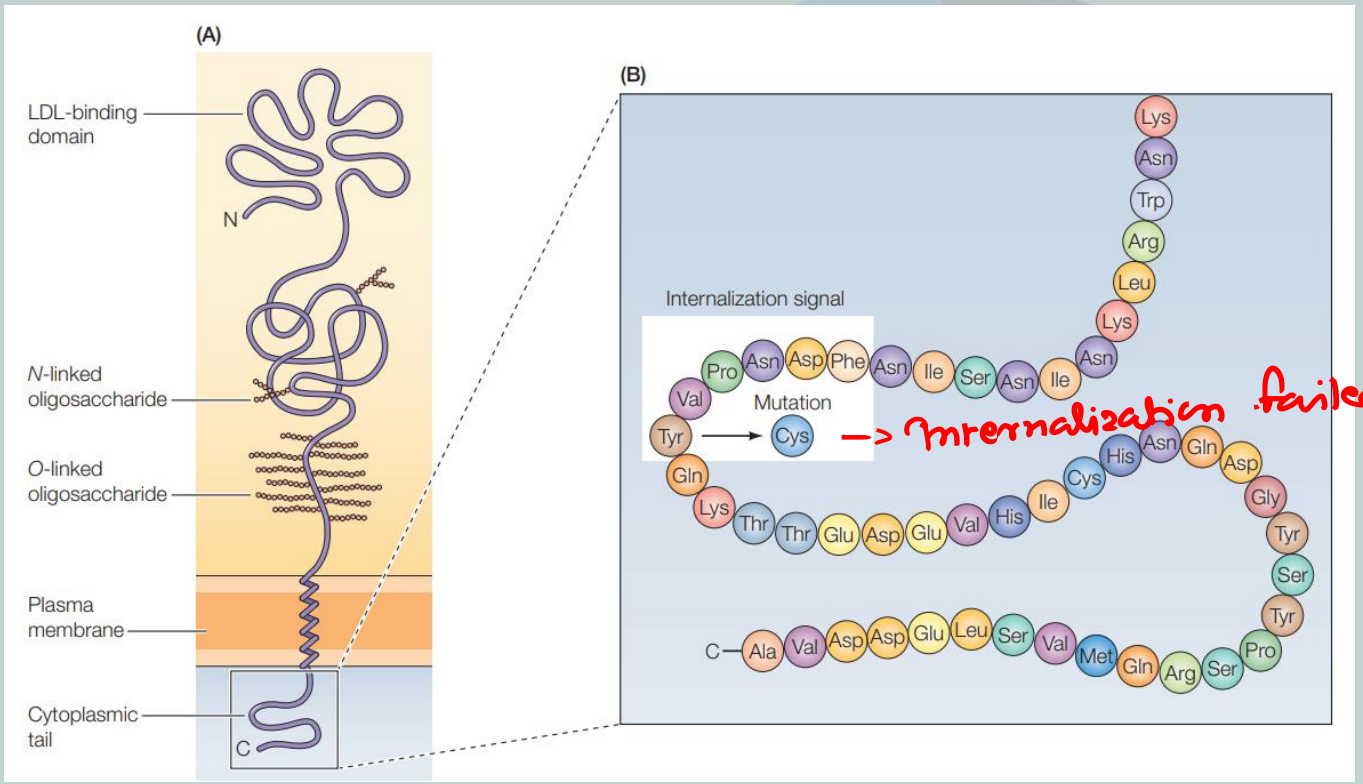
IDL – Intermediate density lipoprotein = Protein = lipid = Intermediate density

LDL – Low density lipoprotein = Protein ↓ : lipid ↑ = Density ↓ = Bad (Cholesterol)

LDL cholesterol is referred to as “bad cholesterol” because it can clog arteries and lead to heart attacks or stroke, particularly when the LDL particles are present in a high concentration.

In contrast, HDL cholesterol is referred as “good cholesterol” because it can remove LDL cholesterol from the arteries.

Specific Receptors for LDL


(A)
LDL-binding domain
N
N-linked oligosaccharide
O-linked oligosaccharide
Plasma membrane
Cytoplasmic tail
C
(B)
Internalization signal
Mutation
Tyr → Cys
Lys Asn Trp Arg Leu Lys Asn Ile Asn Ile Ser Asn Phe Asp Asn Pro Val
Gln Lys Thr Thr Glu Asp Glu Val His Ile Cys His Asn Gln Asp Gly Tyr Ser Tyr Pro Gln Arg Ser Met Val Asp Asp Glu Leu Ser Val Ala C

→ Internalization failed → Familial Hypercholesterolemia

↓

- Autosomal Dominant Disease

- (A)- The LDL receptor includes 700 extracellular amino acids,
- A transmembrane α helix of 22 amino acids,
- and a cytoplasmic tail of 50 amino acids.
- The N-terminal 292 amino acids constitute the LDL-binding domain.

(B) Six amino acids -cytoplasmic tail - internalization signal,

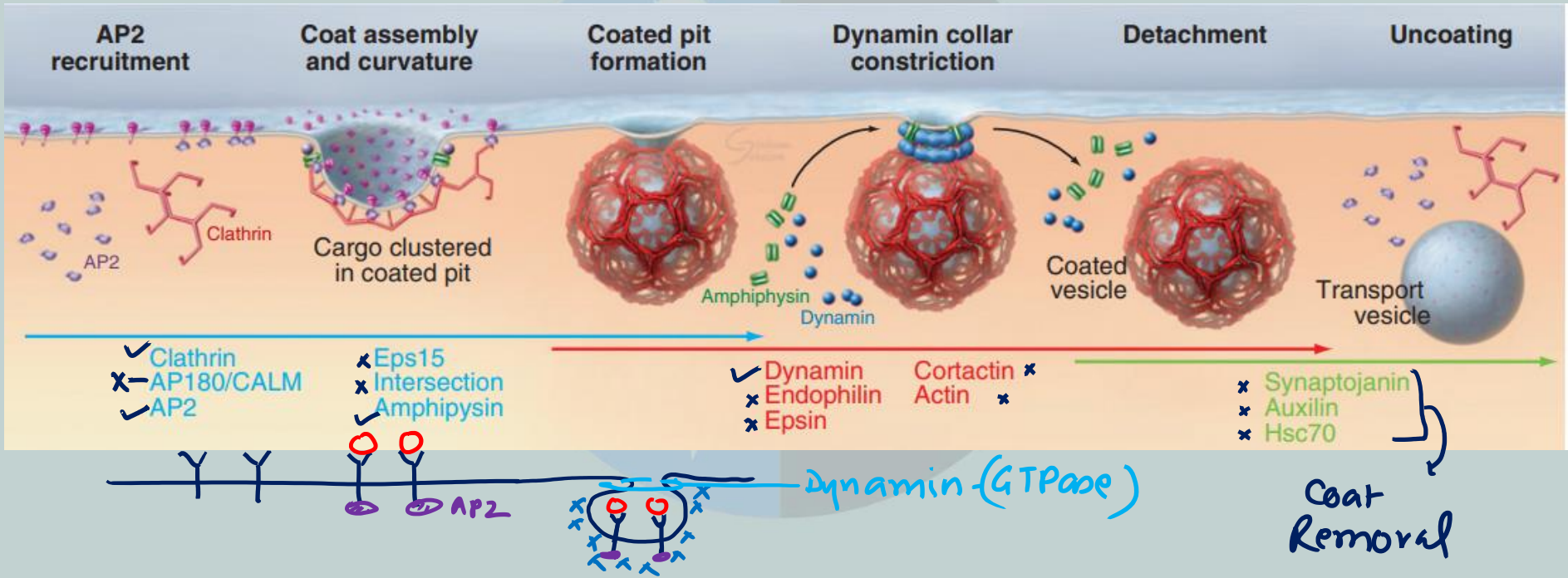
first recognized because the mutation of tyrosine (Tyr) to cysteine (Cys) in a case of familial hypercholesterolemia prevented concentration of the receptor in coated pits

↓

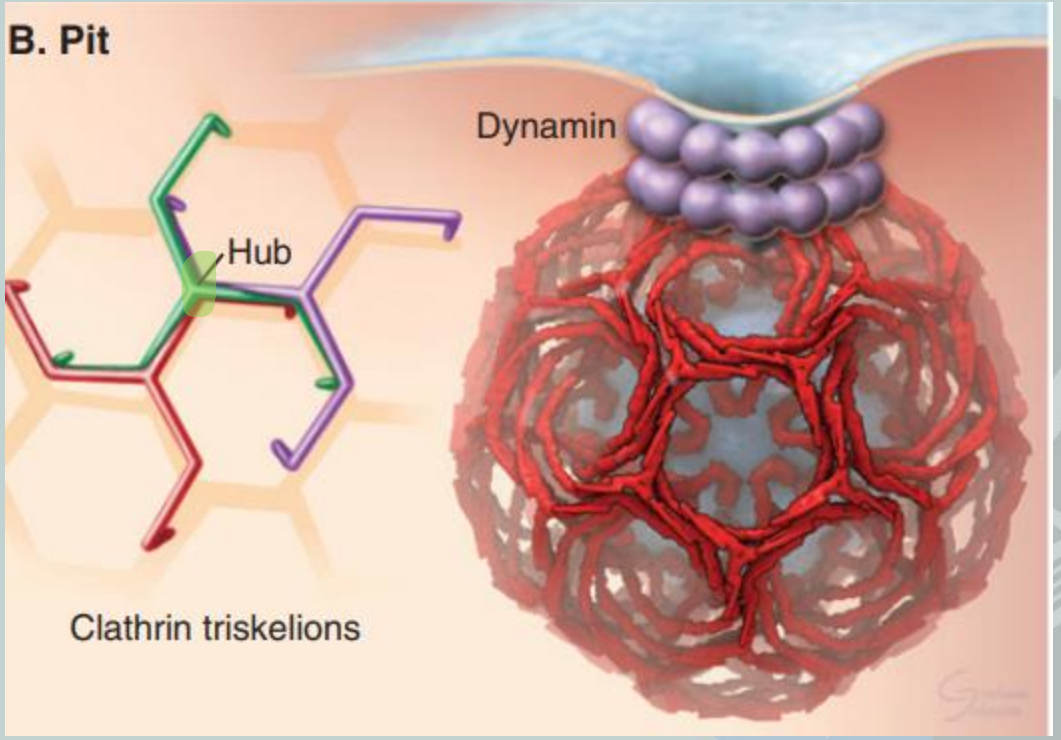
LDL-1se

internalization failed

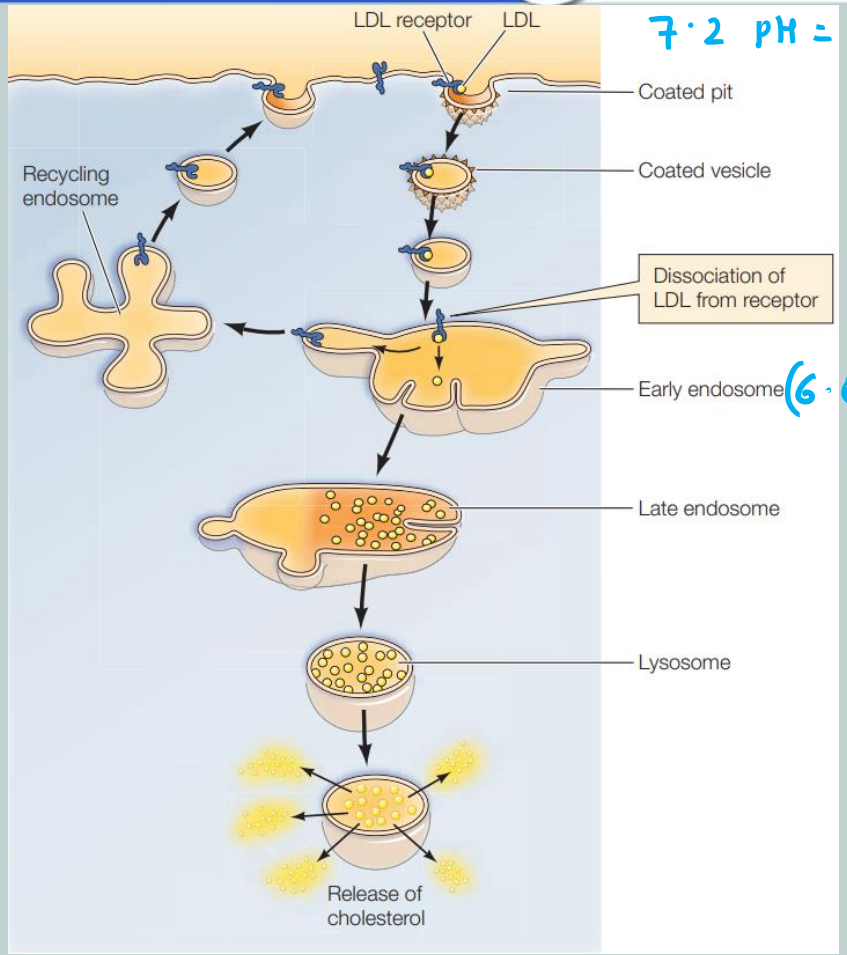
LDL bound to its receptor is internalized in clathrin-coated vesicles,



- . AP2 complexes are targeted to the plasma membrane and interact with tyrosine-based sorting motifs in the cytoplasmic domains of transmembrane proteins.
- AP2 also initiates the assembly of a polygonal lattice of clathrin, which concentrates cargo molecules in coated pits.
- AP2 and clathrin interact with protein amphiphysin, which attracts the guanosine triphosphatase (GTPase) dynamin.
- After assembly of a coated pit and fission of the coated vesicle from the plasma membrane,
- auxilin and the adenosine triphosphatase (ATPase) Hsc70 dissociate clathrin and release the vesicle carrying cargo into the cell for fusion with endosomes



Clathrin-coated pit and the arrangement of clathrin triskelions in the coat.

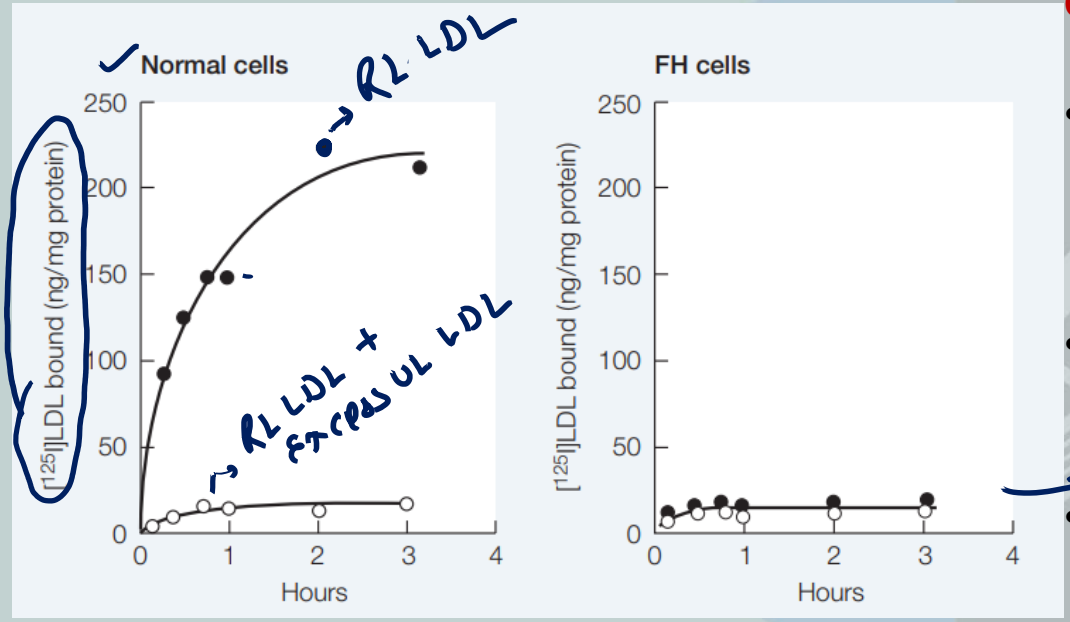


7.2 pH = LDL Binds with its Receptor

(6.8 pH) → dissociation of LDL from its Receptor

Brown and Goldtein reported the results of experiments

Time course of the binding of radioactive LDL to normal and FH cells



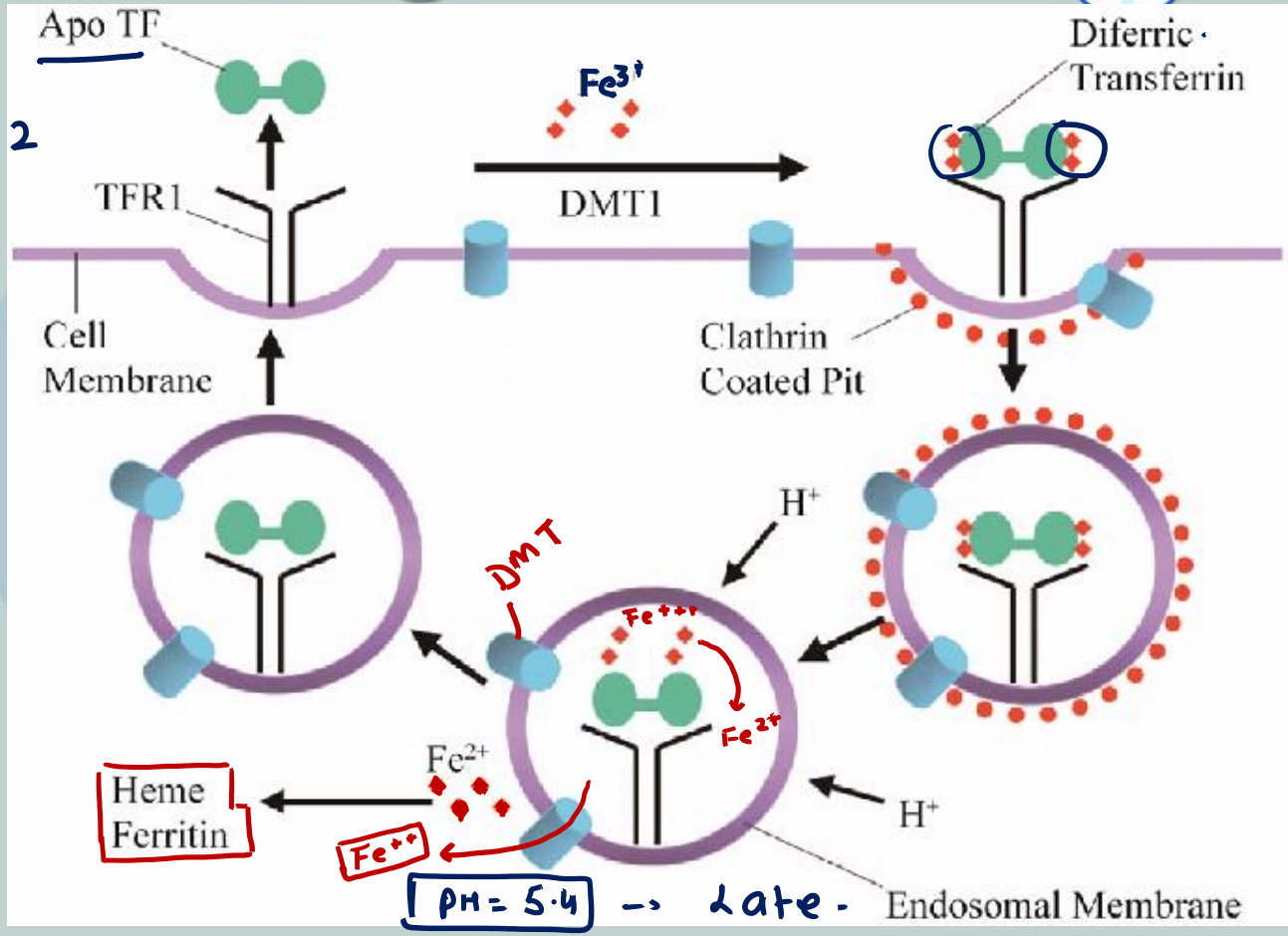
Data are presented as nanograms of LDL bound per milligram of cell protein

- Observe Binding of RL LDL with its Receptor
- Cells were incubated with radioactive [125I]LDL in the presence (open circles)
- or absence (filled circles) of excess unlabeled LDL.
- Cells were then harvested, and the amount of bound radioactive LDL was determined.

Iron Uptake

pH = 7.2

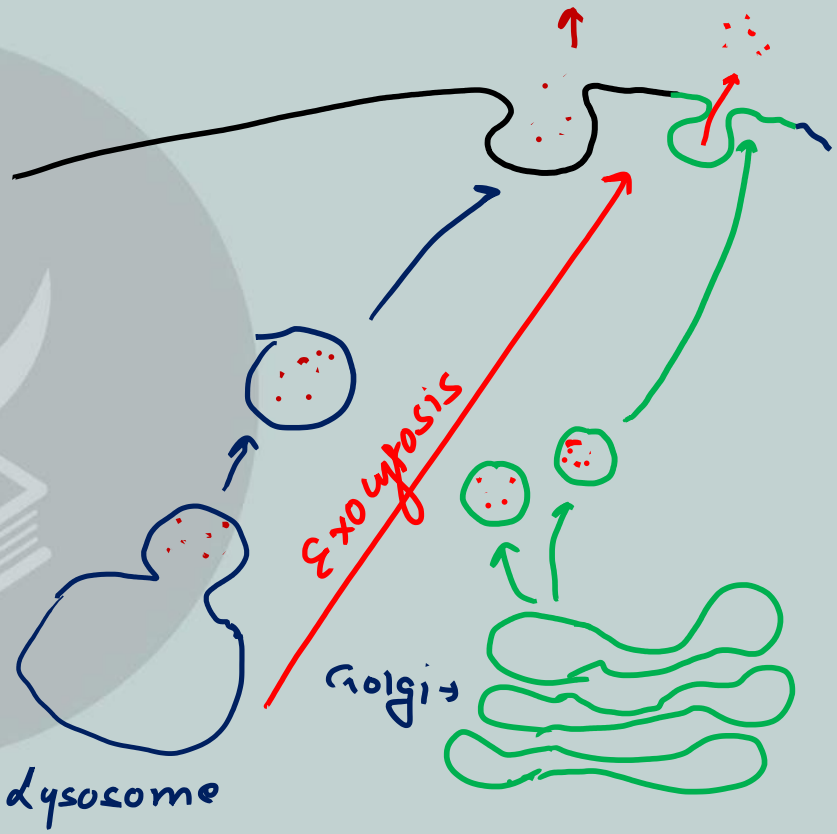
DMT → Di valent metal ion Transporter



Exocytosis

Examples -

- B cell Cells - able to secret antibody
- Pancreatic cell- Enzyme Secretion
- fibroblast cell - Collagen Secretion
- Release of Growth factor
- Neurotransmitter Release
- Cortical Reaction during fertilization



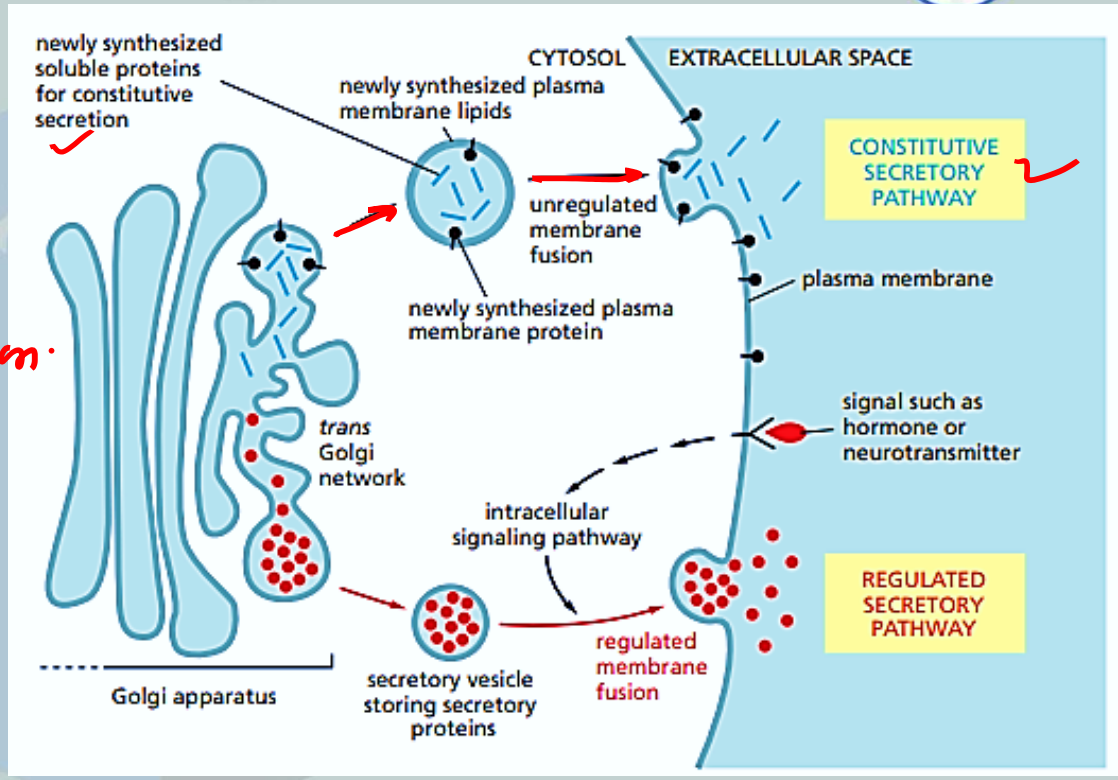
Specialized secretory cells also have a regulated secretory pathway, secretory vesicles, where the proteins are concentrated and stored until an extracellular signal stimulates their secretion.

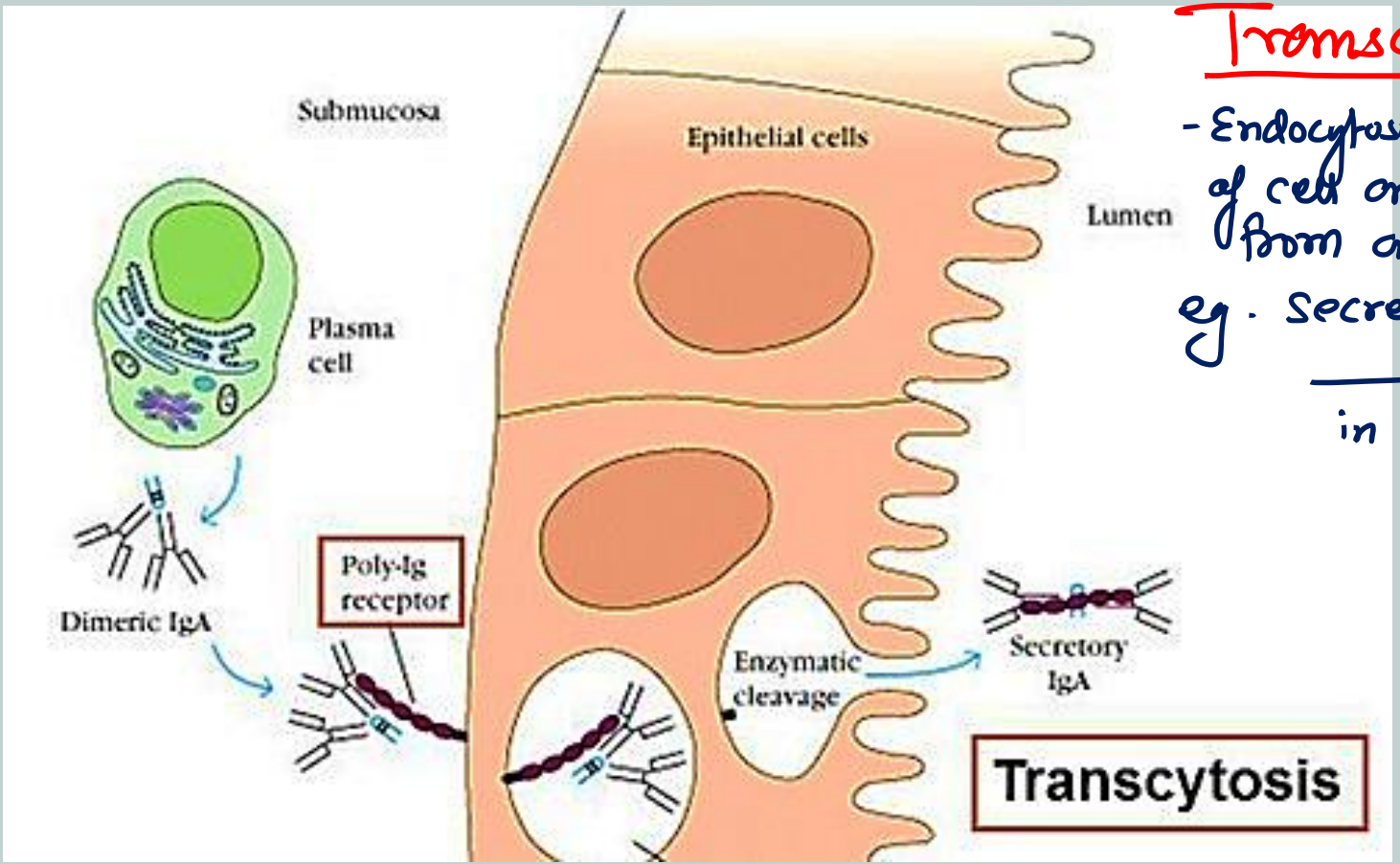
Size ↑

eg- insulin, Antibody } Secretion.

constitutive secretory pathway operates in all cells. Many soluble proteins are continually secreted from the cell by this pathway, which also supplies the plasma membrane with newly synthesized membrane lipids and proteins

vesicle size = ↓ eg. Collagen Secretion.





Transcytosis

- Endocytosis from 1 face of cell and exocytosis from another face

eg. Secretion of IgA in tears or in sweat

Blood IgA

- α chain
- H chain
- J chain

Secretory IgA →

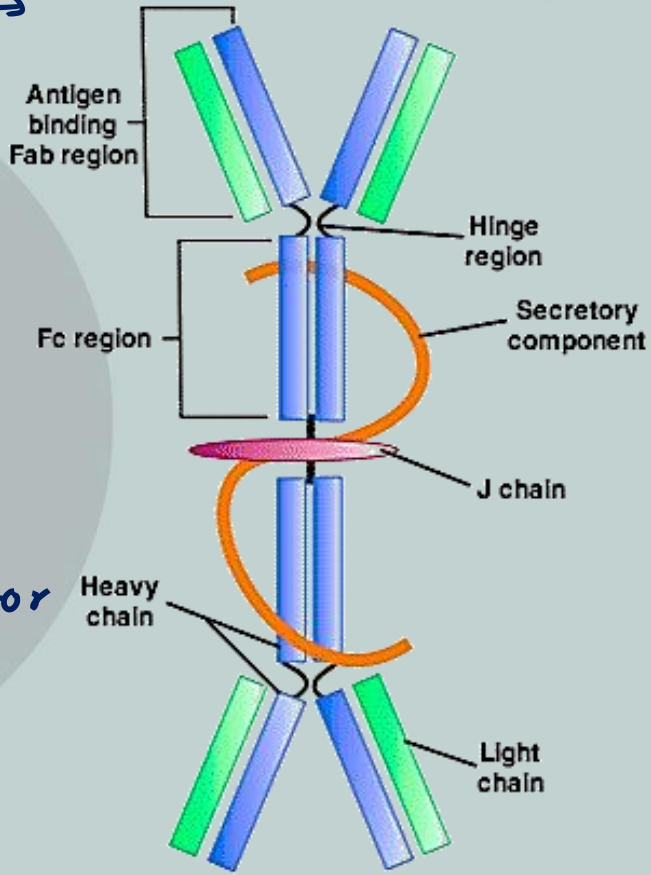
- α chain
- H - Chain
- J - chain
- S - chain

↓

Secretory chain

↓

Part of Receptor



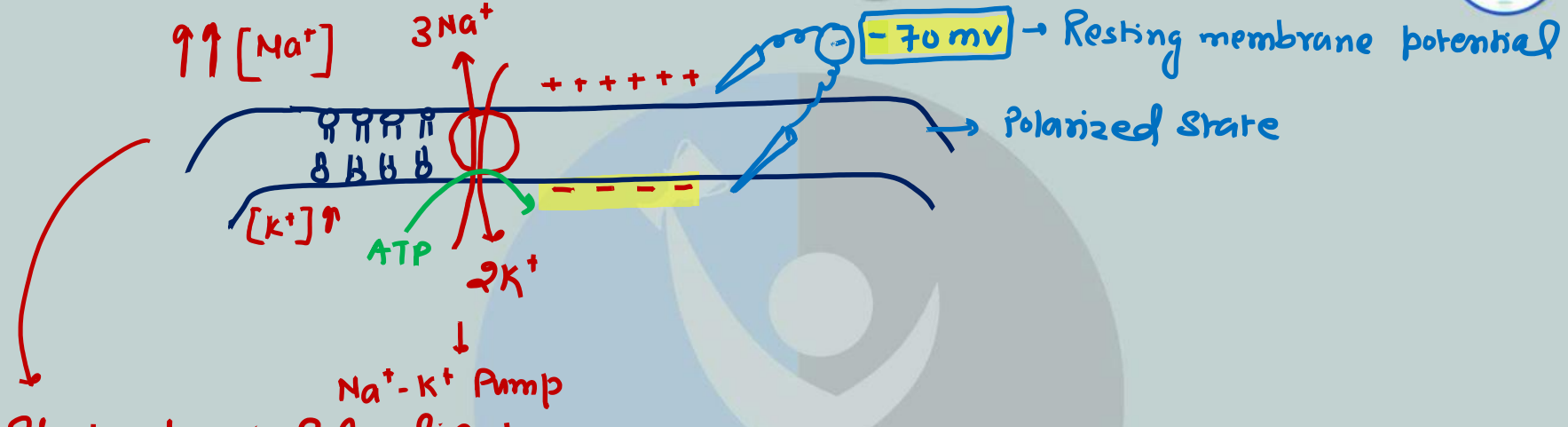
Electrical properties of membrane

- Plasma membrane, are selective permiable for Charged ion
- ions moves Through Particular Transporter
  - Active Pump
  - Passive ion channel.

* Movement of Charged ion Across membrane
  - ↳ is based upon Electrochemical Gradient
* Pump → Generate Electrical potential Cross the membrane.

Transport of charged molecule

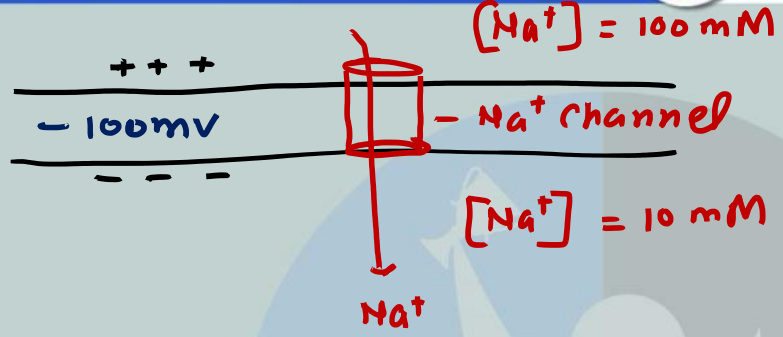
Through movement Ion Channel Charged ion Across The membrane Through ion Channel is depends upon Electrochemical Gradient – Electrical as well as Chemical (Conc.) Gradient



Electrochemical Gradient

- Electrical Gradient = Charge gradient
- Chemical Gradient = Concentration Gradient

Que



- movement of uncharged molecule is along its conc. gradient
- movement of charged ion is Along its Electrochemical Gradient

Na^+ influx = ΔG = Conc. Gradient + Electrical Gradient

ΔG = Electrochemical Gradient.

ΔG inward movement = $2.303 RT \log \frac{C_{in}}{C_{out}} + ZF\Delta E$

$2.303 RT \log \frac{C_{in}}{C_{out}}$: Conc. Gradient

$ZF\Delta E$: Electrical Gradient

ΔG inward movement $= 2.303RT \log \frac{C_{in}}{C_{out}} + 2F\Delta E$

ΔG outward movement $= 2.303RT \log \frac{C_{out}}{C_{in}} + 2F\Delta E$

1.36

- Pressure
- Temp

] constant

C_{out} = Conc. outside the cell

C_{in} = " inside " "

2 = Charge on ion

F = Farrady constant

ΔE = Voltage on membrane.

$$\Delta G_{in} = 1.36 \log \frac{10}{100} + 1 \times 23 (-0.1)$$

$$= 1.36 \log .1 + (-2.3)$$

$$= 1.36 \times (-1) + (-2.3)$$

$$\boxed{\Delta G = -3.66}$$

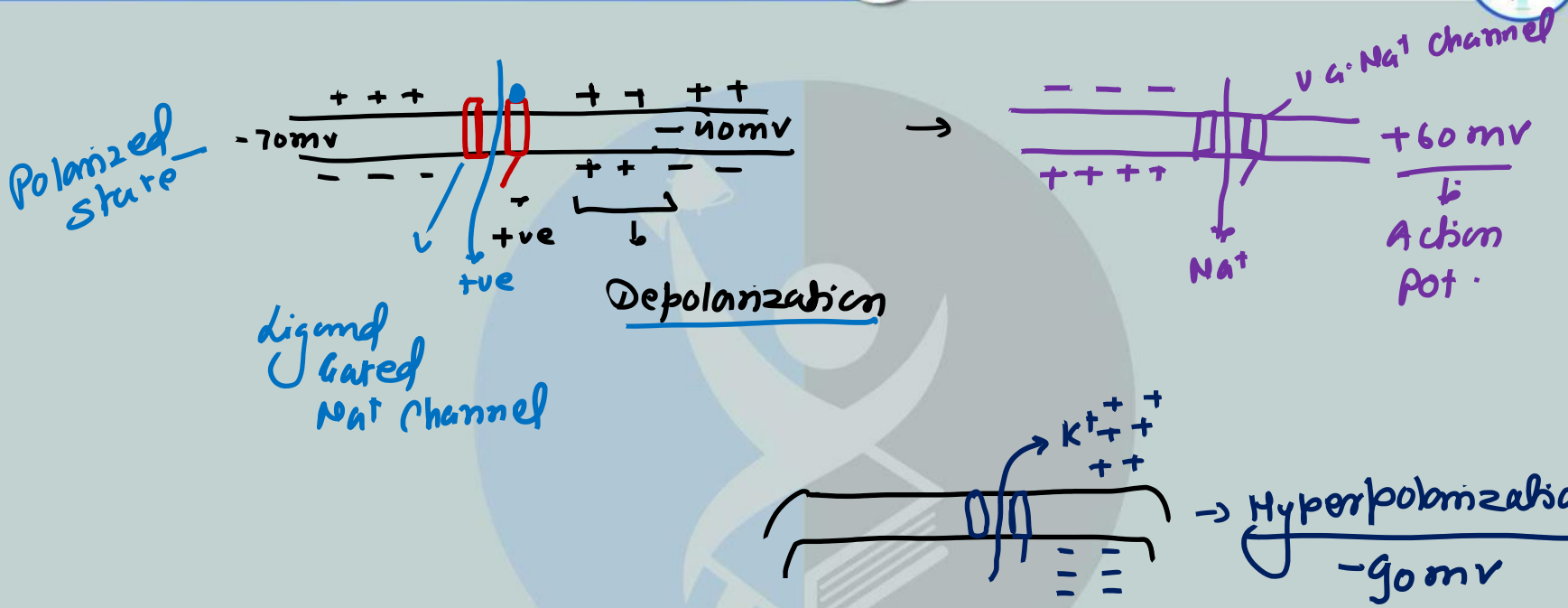
$\Rightarrow$ Na^+ influx - Spontanious.

Equilibrium pot.: Can be Calculate with the help of Nerst equation.

Equilibrium pot. of an ion

- a potential on pm. at which the Net movement of an ion is zero

* Equilibrium pot. of K^+ ion = −90mv → Near value of Resting pot. (−70mv)
* Equilibrium pot. of Na^+ ion = +60mv → value of Action Potential.


Polarized State
-70mv
+40mv
+ve
+ve
Depolarization
Ligand Gated Nat Channel
V G: Na+ channel
+60 mv
Action Pot.
Na+
K+
Hyperpolarization.
-90mv

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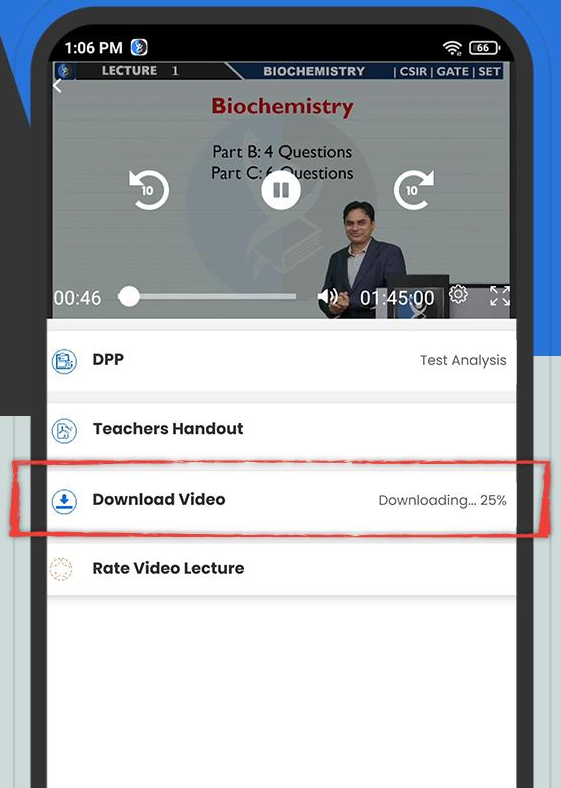

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